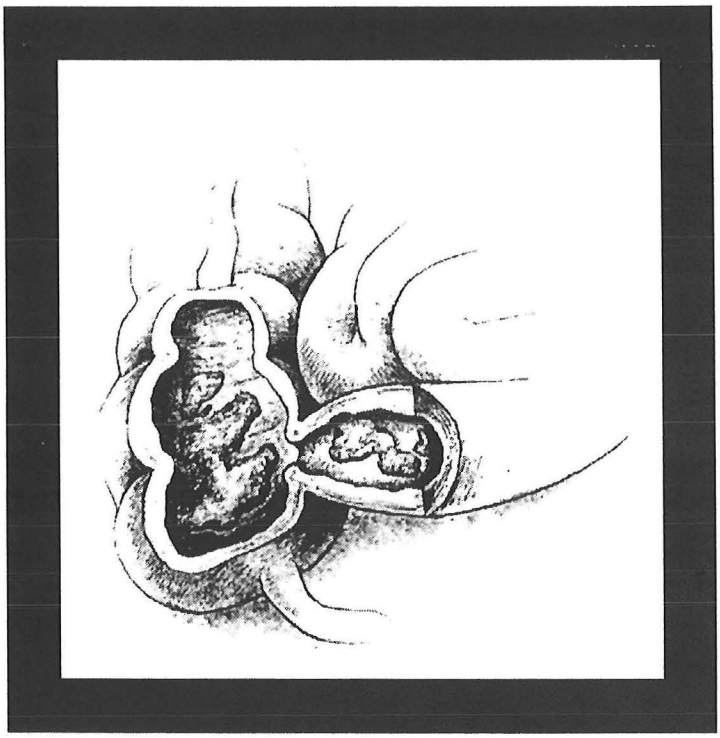
INTERNAL MEDICINE GRAND ROUNDS

SEPTEMBER 6, 2001

Update in Management of Inflammatory Bowel Disease: New Approaches and New Therapies



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Introduction

Inflammatory Bowel Disease (IBD), Crohn's Disease (CD) and Ulcerative Colitis (UC) comprise a group of multi-systemic, relapsing inflammatory diseases of unknown origin. Since ulcerative colitis was first described in 1875, there has been much learned about both of these chronic disorders. These diseases have a worldwide distribution and spare no racial, ethnic, or socioeconomic group.

Because the subject matter is so wide ranging, every aspect of IBD cannot be covered within the scope of this review. Since pathogenesis remains unknown, only very a very brief comment of etiology will be discussed. Most of the recent advances in Inflammatory Bowel Disease have been with regard to new therapies for and new approaches to the IBD patient. Therefore the focus of this review will be to provide update on new therapeutic information in the inflammatory bowel diseases.

Epidemiologic Considerations

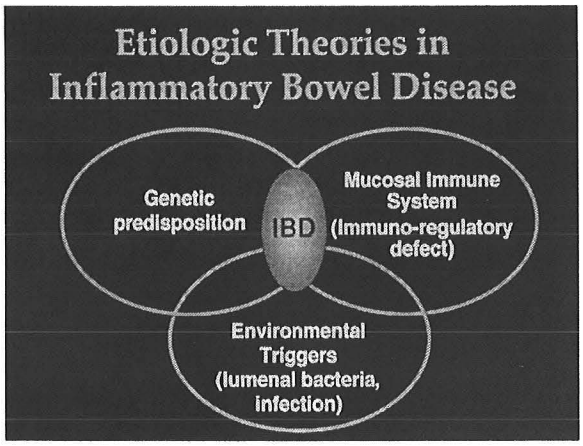
The incidence of IBD varies greatly within geographic areas and within distinct populations. An understanding of the differences within and between different groups has provided insight into possible causative factors.

Epidemiology of Inflammatory Bowel Disease

Variable	Ulcerative Colitis	Crohn's Disease
Incidences rates (per 100,000)	Northern countries: 6-12 Southern countries 2-8	Northern countries: 5-7 Southern countries: 0.1-4
Time trends in incidence	Variable in different geographic regions	Increasing throughout the world
Racial incidence	More frequent in whites	More frequent in whites
Ethnic incidence	More frequent in Jews	More frequent in Jews
Genetic influences	Yes	Yes Putative chromosome 16
Effect of smoking	Decreases risk	Increases risk
Effect of appendectomy	May decrease risk	Effect unknown

Pathogenesis of IBD

The cause(s) Crohn's disease and ulcerative colitis is (are) unknown. It is clear that these diseases comprise heterogeneous inflammatory disorders resulting from chronic up-regulation of the enteric mucosal immune system. Although the exact etiology and pathogenesis of IBD remains elusive, it appears that, in response to environmental triggers, there is chronic activation of the immunoinflammatory cascade in genetically susceptible individuals resulting in chronic mucosal damage.



The chronic relapsing nature of IBD suggests that the inflammation is driven by antigens that are normally present in the environment. In Crohn's disease, the antigenic drive may be bacterial in nature; in ulcerative colitis, it is less certain.

There are several theories of etiology that have some experimental support. The simplest theory is that IBD is a specific, persistent infection, but there is really no good evidence that this is the case. The agents that have been hypothesized include mycobacteria, helicobacter, measles and listeria. Other theories are based on animal models and clinical experimental results. One is that there is a leaky barrier that permits the uptake of bacterial products that overwhelm the normal host defense. Another theory is that there is a host-dependent, dysregulated, overly aggressive immune response that could be mediated by a loss of tolerance.

There is far more evidence of genetic susceptibility in Crohn's disease than in UC. Not only is there increased familial

incidence of disease, but there are familial patterns of disease as well. There is increased concordance of monozygotic versus dizygotic twins. Also, a genome-wide search has implicated chromosomes 12 and 16 in Crohn's disease. HLA-DR_2 has been implicated in ulcerative colitis in some ethnic groups.

Clinical Manifestations

In clinical presentations of IBD, it commonly presents as one of two distinct clinical entities, either ulcerative colitis or Crohn's disease. Some have proposed that they are distinct clinical entities that share difference pathophysiologic processes. In ~10% of cases, however, it is not possible to distinguish UC from CD with certainty. In these cases, the designation, indeterminant colitis is applied.

In ulcerative colitis, the inflammatory process is usually confined to the mucosa of the colon. Inflammation almost always begins in the rectum and extends continuously for a variable extent. Histopathologic features include crypt abscess, depletion of mucin from goblet cells, infiltration of the lamina propria by neutrophils and lymphocytes, and absence of inflammation in the deeper layers of the bowel. Diagnosis is based on characteristic colonoscopic findings of mucosal friability, superficial ulceration and mucopurulent exudate. Patients typically present with bloody diarrhea, but some, particularly those with proctitis, may actually have constipation. The severity of illness is generally proportional to the extent of colonic inflammation.

Crohn's disease is more varied in its clinical manifestation than is ulcerative colitis. Any site within the gastrointestinal tract may be involved. The colon alone is involved in 30%, small intestine in 40%, and both small and large intestine in 30% of patients. Inflammation is typically segmental and discontinuous, and in Crohn's colitis, the rectum may be spared. In contrast to UC, the acute and chronic inflammation of Crohn's disease is typically transmural, extending through all layers of the bowel, and is often asymmetric within the segments of the intestine. Aphthoid ulcers are observed early in the course, whereas superficial, deep linear, and serpiginous ulcerations and fissures indicate more advanced disease. Extensive linear ulceration around islands of normal mucosa may result in a characteristic cobblestone appearance. On histologic examination of endoscopic biopsy specimens, noncaseating granulomas are found in ~25% of patient with Crohn's disease. Submucosal collagen deposition is common and contributes to formation of fistulas and abscesses. Perianal disease may be prominent and characterized by fissures, fistulas and abscesses.

Pathologic and Clinical Features of IBD

Features	Ulcerative colitis	Crohn's Disease
PATHOLOGICAL FEATURES		
Segmental	0	+ +
Transmural involvement	+ / -	+ +
Granulomas	0	+ / + + (50%)
Fibrosis	+	+ +
Fissuring, fistulas	+ / -	+ +
Mesenteric fat, lymph node involvement	0	+ +
CLINICAL FEATURES		
Diarrhea	+ +	+ +
Rectal bleeding	+ +	+
Abdominal pain	+	+ +
Palpable mass	0	+ +
Fistulas	+ / -	+ +
Strictures	+	+ +
Small bowel involvement	+ / - ("backwash ileitis")	+ +
Rectal involvement	+ + (95%)	+ / ++ (50%)
Extraintestinal disease	+ +	+ +
Toxic megacolon	+	+ / -
Recurrence after colectomy	0	+
Malignancy (with long-standing disease)	+	+ / -

0 = never
+ / - = rare
+ = occasional
+ + = frequent, common

Patients with Crohn's disease may present with a spectrum of findings, including right lower quadrant abdominal pain, often with a palpable mass and diarrhea. Obstruction, often of the terminal ileum, may result from inflammation or fibrosis. Overt bleeding is uncommon but may result from deep ulceration. Systemic findings include fever, weight loss, growth retardation in children and nutritional deficiencies. Anemia may result from blood loss, chronic disease or deficiencies in iron, folate or vitamin B_{12}.

Crohn's Disease Activity Index: The CDAI was derived by choosing from among a number of clinical and common laboratory measurements those that best predicted the physician's global assessment of the clinical status of a large group of Crohn's disease patients. It then was validated in another large group of patients. In the past 25 years, the CDAI has been used in over 50 controlled clinical trials. It offers a standardized scale with which to compare patients and their responses over time within clinical trials and everyday practice. It is sufficiently sensitive to changes in clinical status to allow recognition of small therapeutic effect within clinical trials. It requires that the patient keep a diary of stool number and subjective degree of illness for a week prior to the day the index is calculated. These requirements make assessment cumbersome at a single office visit.

Crohn's Disease Activity Index

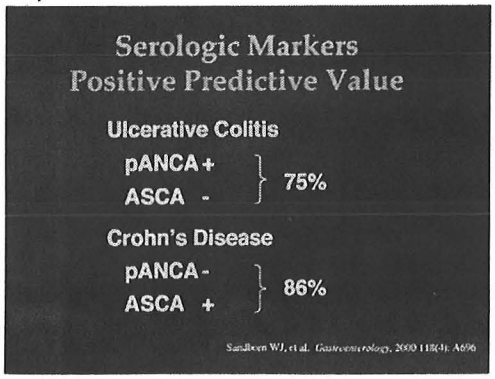
Item (daily sum per week)	Weight
Number of liquid or very soft stools	2
Abdomjnal pain score in 1 week, rating 0-3	5
General well-being (rating 1-4)	7
Sum of findings per week: Arthritis/arthralgia Mucocutaneous lesions (e.g. E. nodosum) Iritis/uveitis Anal disease (fissure, fistula, etc.) External fistula (enterocut./vessicle, etc.) Fever > 36.8°C	20
Antidiarrheal use (eg, diphenoxylate)	30
Abdominal mass (none = 0, equivocal = 2, definite = 5)	10
47 minus hematocrit (males) or 42 minus hematocrit (females)	6
100 x (1 – (body weight divided by standard weight)	1

Serologic Markers in IBD

Although the diagnosis of IBD continues to be based on clinical, endoscopic, histopathologic and radiologic criteria, serologic markers can provide another tool to help diagnose and characterize patients with IBD. Their use is based on the hypothesis that the presence of certain antibodies indicates an underlying dysregulated immune response and the environmental trigger, often bacterial, resulting in IBD. Serologic tests in patients with IBD detect the presence of abnormal antibodies against self or nonself proteins. These serum immune markers are abnormal because these antibodies are not present in healthy persons or in patients with other non-IBD intestinal diseases. As subclinical indicators of immune dysregulation, they are not directly pathogenic to the host but can be used in IBD to stratify patients based on clinical, immunologic, and genetic characteristics and may be useful for predicting response to therapy.

pANCA: Antineutrophil cytoplasmic antibodies (ANCA) were initially described in 1990 after the serendipitous observation that the serum of patients with UC contained antibodies reactive against neutrophils. Unlike the ANCA of other disease states, which is directed against cytoplasmic granules, the ANCA of UC patients shows a perinuclear staining pattern, hence the abbreviation pANCA.

ASCA: Antibodies against baker's yeast, anti-*Saccharomyces cerevisiae* antibodies (ASCA), are present in 50% to 70% of patients with Crohn's disease and only 5 to 10% of patients wit UC. ASCA is only rarely expressed in patients who do note have IBD and thus is highly specific for Crohn's disease. Because self-antigens do not cross react with ASCA, this serum immune marker is not considered an autoantibody. A recent multicenter trial compared assays for pANCA and ASCA in different laboratories. The most useful combinations were a positive pANCA with a negative ASCA (a positive predictive value for ulcerative colitis of 75%), and a negative pANCA with a positive ASCA (a positive predictive value for Crohn's disease of 86%).



pANCA-positive Crohn's disease patients have "UC-like" features, including left sided colitis and endoscopic and histopathologic features typical of UC. The similarity in clinical characteristics between pANCA-positive Crohn's disease and pANCA-positive UC suggests a specific type of mucosal inflammation that may respond similarly to therapy. Patients with pANCA-positive Crohn's disease may have a reduced response to anti-tumor necrosis factor therapy compared to those who are pANCA-negative.

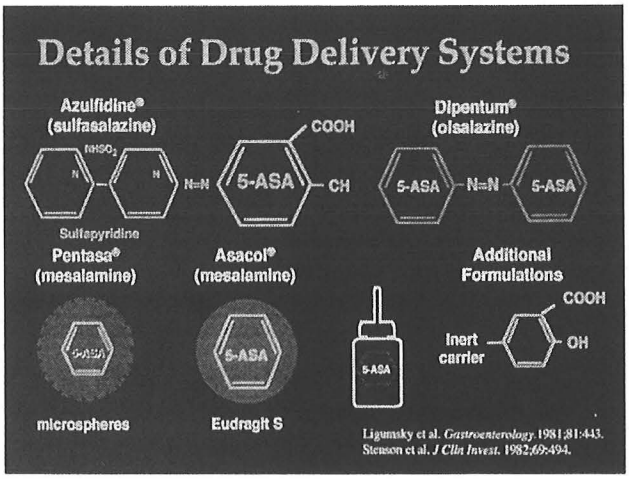
Medical Therapies in IBD

The therapeutic modalities used to treat IBD act at various locations along immune and inflammatory pathways. The general management goals for patients with IBD should begin with a proper diagnosis, followed by prompt therapeutic response, with the goal of inducing complete remission. Although traditional therapies such as aminosalicylates and corticosteroids, continue to be the conerstones in the management of IBD, immunomodualtors, such as azathioprine and 6-mercaptopurine (6-MP), are demonstrating increasing importance in the setting of steroid-resistant and steroid-dependant disease. Furthermore, increasing roles for antibiotics, aminosalicylates and other immunomodulators are being defined.

Aminosalicylates.

Sulfasalazine was first used to treat rheumatoid arthritis and demonstrated an unanticipated reduction of gastrointestinal symptoms in patients with coexistent UC. Sulfasalazine has subsequently been demonstrated to be beneficial for the treatment of UC and CD and, along with the newer 5-aminosalicylates, is the most commonly prescribed medication for IBD.

Sulfasalazine is composed of sulfapyridine linked to 5-aminosaliclyic acid (5-ASA) by an azo-bond. It is poorly absorbed in the upper gastrointestinal tract and is cleaved by colonic bacterial azo-reductases into 5-ASA (mesalamine) and sulfapyridine. The 5-ASA component is poorly absorbed from the colon (approximately 10 to 20%) and is primarily excreted in the feces. The 5-ASA moiety appears to be the active anti-inflammatory component of sulfasalazine, whereas the sulfapyridine moiety, which accounts for most of the drug's toxicity, acts primarily as a carrier for 5-ASA, preventing proximal small bowel absorption and allowing delivery to the colon. The specific mechanism of the anti-inflammatory properties of 5-ASA remains undefined.



Mesalamine. There are several specific therapeutically active mesalamine compounds. Though these agents are generically referred to as mesalamine, they have their differences. The site of delivery in the GI tract differs from one compound to another. For that reason, the pharmaceutical trade name is typically used in prescribing these compounds.

ASA Compounds in IBD

Drug	Site of Delivery	Active Dose	Maintenance Dose
Azo-bond			
Sulfasalazine (Azulfadine)	Colon	4-6 g/day	2-4 g/day
Olsalazine (Dipentum)	Colon	1.5-3 g/day	1.5-3 g/day
Delayed-release			
Asacol	Terminal ileum and colon	2.4-4.8 g/day	0.8-4.8 g/day
Sustained-release			
Pentasa	Small intestine and colon	2-4 g/day	1-3 g/day
Topical			
Mesalamine enema	Left colon	1-4 g qhs	1 g qhs
Mesalamine suppository	Rectum	500 mg b.i.d.	500 mg qhs

Oral mesalamines (5-ASAs) may be useful in certain cases of active UC and in prophylaxis. Olsalazine (Dipentum) which joins two 5-ASA molecules by an azo bond and, like sulfasalazine, requires bacterial degradation in the colon, is as effective against active UC and in maintaining remission in UC. It has not undergone extensive testing in either active or remitted Crohn's colitis. Asacol is a delayed-release tablet form of 5-ASA which is coated with an acrylic resin that dissolves at pH>6.0. It has proved effective in both active and remitted UC and in CD, especially when the ileum is involved. Pentasa is a controlled-release formulation of 5-ASA that is encapsulated in ethyl cellulose microgranules. It has proved effective in active and remitted UC and in active CD regardless of disease location. Pentasa appears to be more effective than placebo in maintaining remission in both small-bowel and colonic CD if begun within 3 months of the onset of remission.

There are considerable data to support the use of 5-ASA preparations in preventing postoperative recurrence of CD, particularly in patients with colitis, with less effect observed in patients with only small-bowel disease. Sulfasalazine and 5-ASA products are safe in pregnant women, and are safer than permitting the disease to be active and allowing for the possibility of surgical intervention during pregnancy

Topically administered preparations (suppositories and enemas) may be preferred for left-sided UC.

The use of mesalamine for active Crohn's disease may be controversial, although certain clinical trials and clinical experience support a favorable response, especially if the colon is involved. In one study of patients with symptomatic Crohn's disease, Asacol (3.2 gm/day) taken for 16 weeks produced remission in 45% of patients, compared to 22% in the placebo group, measured by changes in the CDAI. In another trial with Pentasa, patients with active CD had a remission rate of 43% using the highest dose (4 gm/day), compared with 18% of patients on placebo; patients receiving lower doses of the active drug showed no significant differences in remission from the placebo cohort. Newer mesalamine preparations may be more useful in active Crohn's disease and in the prophylaxis of the disease than sulfasalazine because higher doses may be used with fewer side effects. Some studies suggest that sulfasalazine and the new mesalamine preparations may be more effective in Crohn's disease when the colon is involved.

For remission of IBD, oral mesalamine preparations are extremely effective in the maintenance of remission in ulcerative colitis, and they have a variable response in Crohn's disease. Maintenance therapy needs to be individualized, depending on the following: (1) dose response effect, (2) severity of attacks, (3) response to therapy, (4) history of relapse frequency, (5) cost and compliance issues, and (6) side effects.

As many as 30% of patients discontinue sulfasalazine because of side effects. Common adverse effects include nausea, vomiting, heartburn and diarrhea, and these are dose-related. Other more serious sulfapyridine-related reactions, such as bone marrow toxicity and hemolytic anemia, are rare. Overall, 5-ASA preparations are generally well tolerated, with certain rare adverse effects like nephritis, pancreatitis, pneumonitis, or pericarditis that are shared by both sulfasalazine and the newer aminosalicylate preparations.

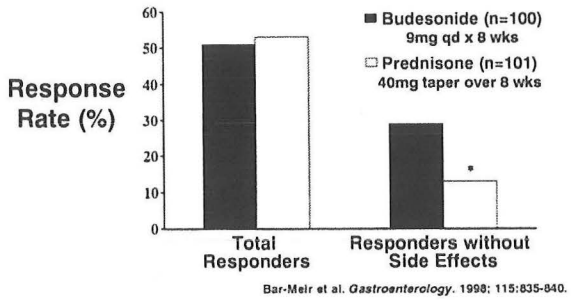
Corticosteroids. Corticosteroids come in topical, oral and intravenous preparations. They have many effects on immune function – inhibiting cellular proliferation, differentiation and migration. They may also inhibit inflammatory mediation via cytokines, prostaglandins, leukotrienes and platelet-activating factors.

Corticosteroids are rarely used alone in the treatment of IBD. If the clinical response to the initial therapy with agents such as 5-ASAs is inadequate, corticosteroids can be added early. If oral steroids fail, intravenous steroids may be used. Corticosteroids have a limited role in the maintenance of remission, or in extraintestinal manifestations or perianal disease. Long-term use of these drugs is not advised.

Newer corticosteroids have first-pass metabolism and, therefore, fewer systemic side effects. Budesonide (see below), for example, is a potent topical antiinflammatory drug that has lower systemic activity than conventional glucocorticoids (it is almost 90% metabolized during its first pass through the liver to forms with minimal or nonexistent steroidal activity).
The incidence of osteoporosis in IBD is approximately 20% to 30%. Steroid use, dose, and duration of treatment are major determinants for the development of osteoporosis; however, osteoporosis may occur in the absence of steroid use.

Budesonide. Budesonide is a synthetic steroid with high affinity for the steroid receptor. After absorption, the drug is metabolized in first pass in the liver and 90% is converted into metabolites with low or no glucocorticoid activity. Because of these characteristics, budesonide can potentially provide efficacious treatment with fewer side effects than conventional steroids. Budesonide (Entocort) controlled ileal release (CIR) capsules deliver the drug mainly to the ileum and ascending colon. This offers a new topical steroid treatment for patients with ileocolic Crohn's disease, with a reduced risk of side effects. Two previous large studies have reported the efficacy of budesonide in the treatment of active CD. Enteric coated formulations of budesonide, 9 mg daily, have been evaluated for treatment of active ileal and ileo-cecal Crohn's disease with consistent benefits comparable to prednisone or prednisolone, 40 mg daily, and superior to placebo.

Efficacy Results and Steroid Side-Effects in Treatment of Active Crohn's Disease



Bar-Meir et al. *Gastroenterology*. 1998; 115:835-840.

In a placebo controlled dose finding study, budesonide CIR capsules were significantly more effective than placebo in inducing remission of active CD affecting the ileum and/or ascending colon, with an optimal dose of 9 mg daily. Budesonide 9 mg daily has also been found to be as effective as oral prednisolone but with fewer side effects. In addition, budesonide significantly prolongs the time to relapse in patients with quiescent disease.

The majority of patients with steroid dependent ileocaecal Crohn's disease may be switched to budesonide controlled ileal release capsules 6 mg without relapse, resulting in a sharp decrease in glucocorticosteroid side effects similar to placebo, and with an increase in plasma cortisol levels. Steroid-related side effects are encountered less often with short-term budesonide compared to prednisolone, but some degree of adrenal suppression can be anticipated.

In summary, patients with moderate-severe Crohn's disease can be treated with prednisone 40-60 mg daily or budesonide 9 mg daily (currently not FDA approved), until resolution of symptoms and resumption of weight gain (generally 7-28 days).

Azathioprine / 6-MP. Two placebo controlled trials demonstrated that azathioprine/6-mercaptopurine are effective for inducing and maintaining remission in patients with Crohn's disease. A study by Markowitz, which evaluated the use of 6-MP in newly diagnosed CD patients, found comparable remission rates in the active drug and placebo groups after 12 weeks; however, at 1 year, there were marked differences between the 2 groups, with 85% of the 6-MP group in continuous remission. The study by Candy, et al., reached similar conclusions, showing that for the long term, (azathioprine) AZA provided a therapeutic advantage over placebo in the maintenance of remission in CD.

Azathioprine/6-Mercaptopurine
Active Crohn's Disease: Maintenance

Study	No.	Duration	AZA/6-MP	Placebo	P	Dose	Concomitant Meds
Candy	63	12 weeks	24/33 (73%)	19/30 (63%)	0.60	AZA 2.5 mg/kg	tapering steroids
		64 weeks	14/33 (42%)	2/30 (7%)	0.001		
Markowitz	55	12 weeks	23/27 (85%)	24/28 (86%)	NS	6-MP 1.5 mg/kg	tapering steroids
		52 weeks	23/27 (85%)	15/28 (54%)	<0.01		

Markowitz study: 12-month prednisone use: 4,641 mg for 6-MP, 7,930 mg for placebo

Candy, *Gut*, 1995; Markowitz, *Gastroenterology*, 2000

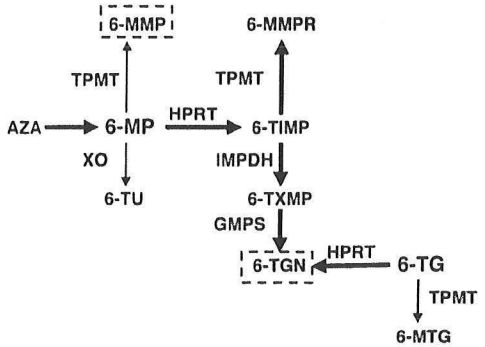
A one-year, placebo-controlled trial found that azathioprine is an effective agent for the maintenance of remission in ulcerative colitis. Patients were randomized to continue on AZA or switch to placebo; withdrawal of AZA led to a significant increase in the relapse rate in the placebo group, compared with those remaining on the active drug.

An important study evaluated the side effects profiles of 396 patients treated with 6-mercaptopurine for inflammatory bowel disease. Infectious complications were seen in more than 7% of patients, and about one-quarter were severe; all infections were reversible with no deaths. Bone marrow depression and pancreatitis were also identified.

Azathioprine is non-enzymatically converted to 6-mercaptopurine. 6-MP can then be inactivated by thiopurine methyltransferase (TPMT) to 6-methyl-mercaptopurine, or alternatively by xanthine-oxidase (XO) to 6-thiouric acid. 6-MP is activated through several enzymatic steps to 6-thioguanine nucleotide. Thiopurine methyltransferase activity is genetically determined, and patients can have low, intermediate or high activity.

A recent study of pediatric patients with IBD sought to determine optimal therapeutic 6-mercaptopurine (6-MP) metabolite levels, and their correlation with factors such as drug-related toxicity and TPMT genotype. The researchers demonstrated that patients with higher concentrations of 6-TGN (6-thioguanine nucleotide) were more likely to respond to therapy with 6-MP. There was no apparent relationship between therapeutic response and achieving leukopenia. Patients with low or intermediate TPMT enzyme activity had higher median 6-TGN concentrations than patients with high (normal) TPMT enzyme activity.

Metabolism of Azathioprine and 6-MP



Immunosuppressive with azathioprine/6-MP therapy is indicated for patients with ulcerative colitis in a number of circumstances. For example, steroid-dependent patients may be candidates for AZA/6-MP; these drugs may also be

appropriate for the maintenance of remission.

Using 6-TG and 6MMP metabolite levels, one can define patients who may go into remission, and those who may fail or may experience toxicity. Thus, in patients with preferential metabolism of azathioprine/6-MP to 6-MMP through high levels of the TPMT enzyme, they generally do not respond to AZA/6-MP or develop hepatotoxicity or leukopenia. In contrast, among patients who preferentially metabolize the drug to 6-TG or 6-TGN, and can achieve appropriate levels of this metabolite relative to 6-MMP, they tend to enter remission.

For those patients in whom the TPMT enzyme prevents them from getting an adequate level of 6-thioguanine, there is experimental support for clinical administration of 6-TGN. In a study with 6-thioguanine, patients responded by 4 weeks following initiation of the compound. This drug does not use the TPMT enzyme, and achieves a therapeutic level without inducing toxicity. There may be a more rapid onset of effect than is seen with the classic thiopurines (azathioprine, 6-mercaptopurine).

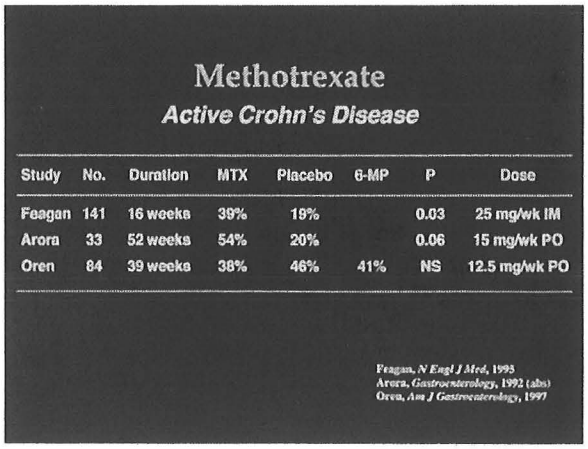
Patients treated with 6-MP or AZA can be divided into 3 groups:

- Those who do not achieve an adequate level of 6-TGN, which may be due to low dose, malabsorption, or noncompliance.
- Those who are6-MP-resistant; they cannot achieve an adequate level of 6-TGN because they preferentially metabolize the drug to high levels of 6-MMP.
- Those who are refractory to 6-MP; they do achieve an adequate level of 6-TGN, and do not respond to the drug.

Methotrexate. First line immunomodulatory therapy, given to initiate and maintain remission and allow tapering of steroid therapy, is usually azathioprine or 6-mercaptopurine. Unfortunately, approximately 20% of patients are resistant to or intolerant of thiopurines, and their management provides a difficult therapeutic challenge.

Methotrexate and its breakdown products inhibit several enzymes in the metabolic pathway of folic acid. While the cytotoxic and antiproliferative effects of high dose methotrexate are ascribed to inhibition of dihydrofolate reductase, with consequent inhibition of DNA, RNA, and protein synthesis, the anti-inflammatory and immunomodulatory actions of low doses are probably due to inhibition of other folate dependent enzymes.

Three studies shown in the figure below detail the use of oral or intramuscular methotrexate for active Crohn's disease. Researchers found that 15 mg per week orally and 25 mg per week IM are effective therapies for active CD. For example, Feagan, et al., reported that 39% of chronically active CD patients achieved clinical remission after 16 weeks of weekly injections of MTX, compared to 19% in the placebo group. In the study by Arora, et al., oral MTX was associated with fewer disease flares in patients with refractory CD, compared to placebo.



Toxicity, primarily rash, diarrhea, stomatitis, bone marrow suppression, increased liver tests and hepatic fibrosis, have been limiting factors with use of MTX. Oral administration of methotrexate seems to increase the

incidence of gastrointestinal side effects, particularly within 24 hours of dosing, but would be more convenient than injections if proven efficacious.

Immunosuppressive therapy with MTX may be indicated for patients with Crohn's disease as described above. For example, MTX's indications are for patients with mild/moderate inflammatory CD (steroid-refractory), steroid-dependent CD, and remission maintenance.

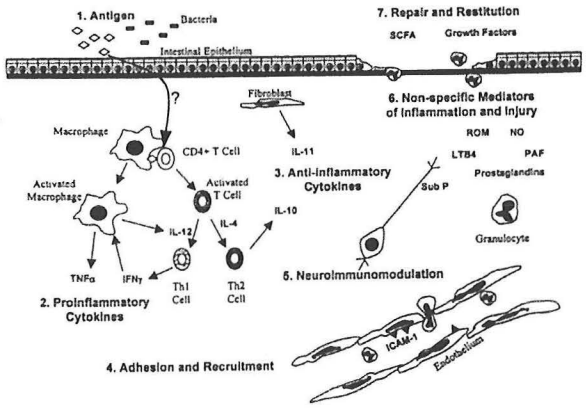
Cyclosporine. IV cyclosporine has been administered to patients with severe steroid-refractory ulcerative colitis. IV cyclosporine appears to be an effective therapy for severe UC. One study found that 82% of patients on cyclosporine showed marked improvement, compared to 0% on placebo; all patients in the placebo group who later received cyclosporine therapy had a response.

Oral cyclosporine has been evaluated in Crohn's disease disease. Overall, studies indicate that low-dose oral cyclosporine is not effective for CD. IV cyclosporine has been evaluated only in uncontrolled trials in patients with severe CD and refractory fistulas with results that indicate response rates of 60 to 80%. Toxicity has been associated with the use of intravenous cyclosporine therapy for ulcerative colitis and Crohn's disease. Because of its known toxicities, cyclosporine has been used with restraint in the treatment of IBD.

Antigen-Directed Therapies

Animal models of colitis have pointed to the intestinal flora as the primary stimulus for inflammation in the gastrointestinal tract. Although it is formally difficult to exclude the role of an unrecognized, pathogenic microorganism, nonpathogenic bacterial species appear to be sufficient to promote inflammation in the genetically susceptible host. It is not known whether the host flora stimulate an immune response through specific antigenic stimuli or in a relatively nonspecific manner transduced through the intestinal epithelium. Nevertheless, manipulation of the intestinal bacteria flora may be beneficial in the treatment of IBD.

Therapeutic Targets in IBD



Antibiotic Therapy. It is now well accepted that bacteria play an important role in the pathogenesis of CD. Antibiotics have long been used in the treatment of Crohn's disease on an empiric basis, although there have been relatively few controlled trials. Well-described indications for the use of antibiotics in CD include perineal disease, localized peritonitis due to micro-perforation, and bacterial overgrowth secondary to a chronic stricture, as well as a useful adjunct to drainage therapy for abscesses and fistulae. While antibiotics appear to have little effect in UC, several controlled trials have demonstrated clinical benefit with metronidazole and/or ciprofloxacin in treating mildly to moderately active CD, particularly in patients with colonic disease.

A single study of oral tobramycin in ulcerative colitis found a 1-week course to be beneficial in achieving complete symptomatic remission; the benefit,

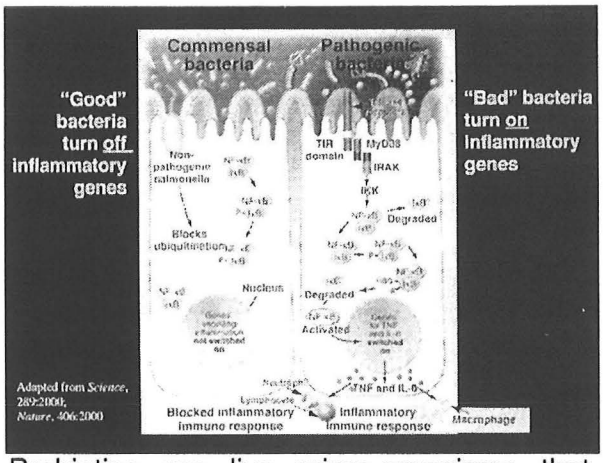
however, was not lasting. In contrast, a study of ciprofloxacin in ulcerative colitis did not suggest additional benefit in induction of remission in combination with corticosteroids. In a separate study, patients with active disease despite other treatments (including oral corticosteroids in half) were continued on prednisone and mesalamine and randomized to additional ciprofloxacin or placebo for 6 months. Only 21% of ciprofloxacin-treated patients failed therapy at 6 months versus 44% of the placebo group (P=.02). It is not known which species may be targeted by these varied antibiotic regimens or whether nonspecific immunomodulatory effects, such as those with quinolones, might contribute to their efficacy.

Antibiotics should be considered in patients not responding to 5-ASA prior to initiation of steroid therapy. Three-month metronidazole therapy has been shown to decrease the severity of early recurrence of CD in the neoterminal ileum and to reduce significantly the clinical recurrence rate at 1 year. . Unfortunately, the toxicity of metronidazole, particularly the occurrence of peripheral neuropathy, limits the duration of its use.

There is currently no evidence that antibiotic therapy is either effective for isolated small-bowel CD, or more effective than sulfasalazine or 5-ASA against CD. Future placebo-controlled trials are needed to determine if there is a permanent place for the use of antibiotics in treating active CD.

The role of mycobacteria in Crohn's disease remains controversial. Consistent demonstration of the organism and well-controlled and blinded clinical trials of antimycobacterial therapy are lacking. A small, randomized, placebo-controlled pilot study of clarithromycin in Crohn's disease generated intriguing data. Five or seven patients receiving clarithromycin achieved remission by 3 months versus 1 year, and it was speculated that the activity was directed against putative infection with *Mycobacterium paratuberculosis*. An open-label study of clarithromycin also appeared to demonstrate reduced symptoms of Crohn's disease, but no larger, double-blind, randomized studies have been reported to confirm these promising data. The combination of rifabutin and a macrolide antibiotic (azithromycin or clarithromycin) was reported to yield benefit over the course of a 2-year study in Crohn's disease.

Probiotic Therapy. Although the disease-causing components of the native gut flora have yet to be identified, the notion of beneficial and harmful flora has been proposed.



Probiotics are live micro-organisms that alter the enteric microflora and have a beneficial effect on health. Bacteria associated with probiotic activity have frequently been lactobacilli or bifidobacteria, but *E. coli* and enterococcal strains have been used, as have non-bacterial organisms such as *Saccharomyces boulardii.* Potential mechanisms of probiotic action include competitive interactions, production of antimicrobial metabolites, dialogue with the epithelium, and immune modulation.

Two studies, one in Crohn's disease and one in ulcerative colitis, have reported prevention of relapse by a nonpathogenic *Escherichia coli* strain. Similar relapse rates were seen among patients with ulcerative colitis randomized to mesalamine or to

receive *E. coli* strain Nissle 1917 (11.3% mesalazine, 16.0% *E. coli* Nissle 1917; P=.12). A similar time to relapse was also observed. Treatment was well tolerated.

Tumor Necrosis Factor-α

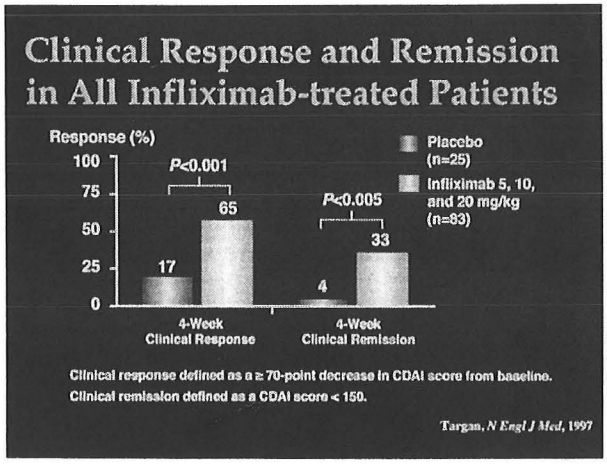
Tumor necrosis factor (TNF)-α is a key inflammatory cytokine possessing many properties relevant to intestinal inflammation. The product of activated macrophages, it is capable of activating other macrophages and priming neutrophils, inducing proteases critical to tissue destruction, enhancing chloride secretion from intestinal epithelial cells, increasing epithelial permeability, and adhesion molecules, thereby contributing to the recruitment of monocytes, lymphocytes, and granulocytes. The expression of TNF-α is increased in both animal models of colitis and human IBD. Approaches to blocking TNF-α in IBD have been studied in some detail with dramatic successes reported in Crohn's disease.

Infliximab

Infliximab is a chimeric monoclonal antibody to human tumor necrosis factor-α (TNF-α), a proinflammatory cytokine which plays an important role in the pathogenesis of CD. Studies with infliximab [(Remicade), called *c*A2 in early published studies] provided the first such data. Controlled trials have demonstrated efficacy for infliximab in moderately to severely active CD and fistulizing CD with sufficient evidence for safety and efficacy for recent Food and Drug Administration approval. Clinical response is rapid, usually within 1 to 2 weeks, and the duration of response ranges from 8 to 12 weeks per infusion.

Early open-label studies produced rapid responses accompanied in many cases by mucosal healing demonstrated on colonoscopy. A subsequent dose escalation study showed a dose of 1 mg/kg body weight to be largely ineffective, with only 20% of patients responding at 12 weeks after a single infusion. Relatively large doses of 5, 10, or 20 mg/kg produced 12-week responses in 50% to 80% of patients. Rigorous grading of the mucosal appearance on colonoscopy again confirmed the ability of this agent to produce rapid healing within 4 weeks of treatment.

The first double-blind, placebo-controlled study of infliximab included 108 patients with active symptoms despite treatment with other medications. All patients had moderate-to-severe disease. Enrolled patients had previously failed methotrexate, cyclosporine, 6-mercaptopurine, or azathioprine or had continued symptoms while on prednisone, 6-mercaptopurine, azathioprine, or a 5-ASA agent. Patients were randomized to an infusion of 5, 10, or 20 mg/kg infliximab or placebo.

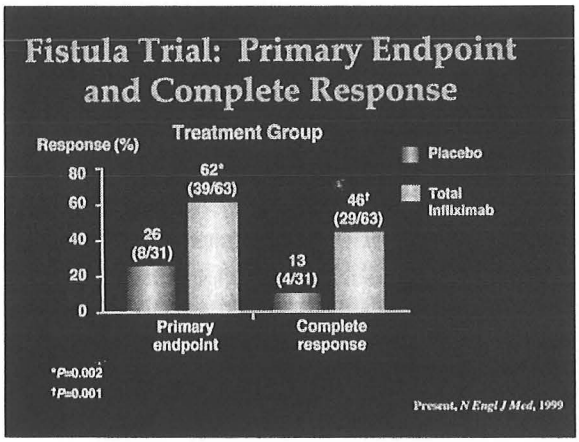


Overall, 65% of patients treated with infliximab achieved a clinical response at week 4, defined as a drop from the baseline Crohn's Disease Activity Index (CDAI) score of 70 or more points. This result was highly statistically significant compared to the placebo response rate of 17%. Nearly all responses were seen within 2 weeks of infusion. Higher doses were not superior. The clinical response among patients treated with 5 mg/kg was 81%, whereas patients treated with 10 or 20 mg/kg had response rates of 50% and 64%. Although these differences are not statistically

distinguishable, it is suggested that the lowest dose studied was at least as effective as higher doses.

An instructive feature of this study was the provision of open-label treatment to patients who had not responded to the initial infusion. Patients who had not responded by 4 weeks from their initial treatment received infliximab at 10 mg/kg. Among the group of 37 patients who did not respond to initial therapy were 14 patients who had initially received infliximab. These patients were far less likely to respond to a second infusion than those who had initially received placebo. Clinical characteristics, such as duration of disease, concomitant treatment, anatomic distribution, sex, and age, have not been found to predict response. Taken together, these findings suggest that basic features of pathogenesis may vary among patients identified as having Crohn's disease. Preliminary evidence suggests that certain TNF genotypes correlate with increased expression of TNF in Crohn's disease, perhaps correlating with response. These findings may substantiate the claim that Crohn's disease represents multiple, distinct processes with one clinical manifestation.

A number of patients in earlier studies had been observed to have closure of enterocutaneous fistulas after treatment with infliximab. Consequently a randomized, placebo-controlled, double-blinded study of infliximab in healing of Crohn's disease fistulas was undertaken. Patients with one or more draining enterocutaneous fistulas were randomized to received infliximab 5 mg/kg or 10 mg/kg or placebo at weeks 0, 2, and 6 and were observed for 26 weeks. Of the 94 patients enrolled, 90% had perianal fistulas; the remaining patients had fistula to other cutaneous surfaces. The primary endpoint was the proportion of patients who experienced a clinical response, defined as a 50% reduction from baseline in the number of draining fistulas for at least 1 month, without an increase in medication or surgery for Crohn's disease. Sixty-eight percent of patients in the 5 mg/kg infliximab arm had a clinical response versus 26% of patients treated with placebo (P=.002); 56% of patients in the 10 mg/kg arm achieved a clinical response. The median time to onset of response was 12 weeks. This was the first double-blind, placebo-controlled demonstration of the efficacy of any agent in healing of fistula.



CDP571

CDP571 is a humanized anti-TNF-α monoclonal antibody of IgG4 isotype. A small, double-blind, placebo-referenced trial in Crohn's disease has been reported. Thirty-one patients with active Crohn's disease were randomly assigned to a single infusion of CDP571 5 mg/kg (21 patients) versus placebo (10 patients). Two weeks after treatment, there was a significant drop from in the mean CDAI from 263 to 167 in the treated patients but not in the placebo group. The mean response was not observed beyond 2 weeks, perhaps reflecting serum concentrations of antibody. Adverse events occurred with similar frequency in the CDP571 and placebo-treated groups. One third of patients developed antibodies against CDP571, but no allergic reactions were noted.

Anti-TNF-α Antibody and Ulcerative Colitis

Few data are available defining the role of TNF-α in ulcerative colitis, and only limited published data are available on the use of anti-TNF-α antibodies in ulcerative colitis. Preliminary studies suggest that infliximab may be of benefit in severe UC, but further studies are needed to prove efficacy.

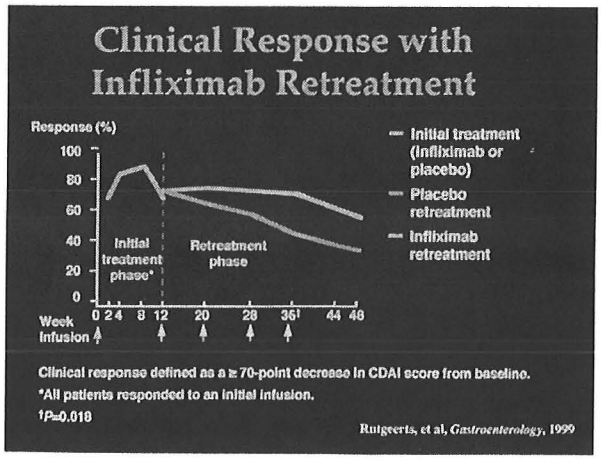
CDP571 has been reported to be beneficial in the cotton-top tamarin model of colitis. An uncontrolled trial of CDP571 in 15 patients with ulcerative colitis produced a variable response. Six of nine patients not receiving corticosteroids and 4 of 6 patients considered refractory to 40 mg of prednisolone experienced a reduction in symptoms, C-reactive protein, and sigmoidoscopic score, although few appear to have had a dramatic response. Information on infliximab in ulcerative colitis is limited to eight patients who participated in a double-blind, placebo-controlled protocol in hospitalized, steroid-refractory patients, which did not complete enrollment. Response was variable, but four of eight infliximab-treated patients (versus none of three placebo-treated patients) were considered successes. The considerable heterogeneity in individual responses may again reflect subclinical heterogeneity in patients with a clinical diagnosis of ulcerative colitis.

Maintenance Therapy and Safety Experience with anti-TNF-α therapy

Despite efforts to minimize the antigenicity of monoclonal antibodies, a major concern remains their immunogenicity. Chimeric antibodies retain approximately 25% murine protein residues. Even *humanized* antibodies, which retain murine sequence in less than 5% of the antibody sequence, may generate host immune responses. Toxicities observed with anti-TNF-α therapy have included formation of human antichimeric antibodies (HACA). With repeated treatment, drawbacks of immunogenicity could include diminishing response or increasing adverse events.

In some cases minor and severe infusion reactions occur. Formation of autoantibodies, leading in some instances to drug-induced lupus may be seen. And a serum sickness-like, delayed hypersensitivity reaction can be observed in some patients re-treated with infliximab 2 to 4 years after initial treatment. The true risk of non-Hodgkin's lymphoma remains to be determined after larger populations are studied over longer periods of time. Recent studies (ACCENT trial) have reported infliximab's efficacy as a steroid-sparing agent. Future studies will need to define the optimal timing and duration of anti-TNF-α therapy, and the utility of continuing other medical treatments.

Limited experience with repeated dosing for maintenance of effect has been reported with infliximab. Seventy-three patients who had a clinical response at 8 weeks in the double-blinded study by Targan et al. described earlier were randomized at week 12 to receive placebo or infliximab 10 mg/kg every 8 weeks for four additional infusions. By 8 weeks after the last infusion (week 44), 65% of patients had a clinical response versus only 37% of placebo-retreated patients (P=.086). Fifty-three percent of infliximab-retreated patients versus 20% of placebo-retreated patients were observed to meet criteria for clinical remission at week 44 (P=.013).



Three of 37 patients who received repeated treatment with infliximab developed human antichimeric antibodies (HACA). One of these patients received repeated doses of drug without apparent detriment. A second developed an immediate hypersensitivity reaction consisting of dyspnea during an infusion. The third patient developed a clinical constellation consistent with lupus arthritis. This study suggests that the development of HACA may ultimately limit the safety of repeated infusions in some patients. No information is yet available regarding the safety, tolerability, or efficacy of repeated dosing with CDP571.

Some general safety concerns are raised by the blockade of TNF-α. The ability of TNF and other members of its family to induce apoptosis in some cells may be another property critical to understanding the side-effect profile of anti- TNF-α agents. A syndrome of lymphoproliferation and autoimmunity is observed in mice with mutations of Fas-Fas ligand, indicating a failure of apoptosis. In these models, lymphocyte populations with abnormal surface markers expand, while self-reactive T cells are not deleted. Mice deficient in the 55-kD TNF receptor do not exhibit lymphoproliferative disease but exhibit diminished responses to lipopolysaccharide and increased lethality to lyse cells infected with virus, another property of TNF, may also be a critical host defense.

Although somewhat greater numbers of infections have been reported after treatment with infliximab, these have been generally mild. The sponsor has recently change the package insert to reflect a risk of reactivation of tuberculosis or risk for histoplasmosis in patients receiving infliximab. Assessment of the effects of infliximab in patients with Hepatitis C infection is currently under evaluation.

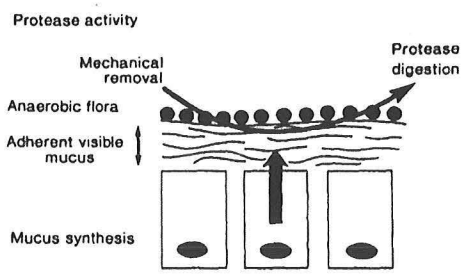
Of the 394 patients include in the safety database submitted for examination by the Food and Drug Administration during the approval process of infliximab, 4 developed lymphoma. This included one patient with Crohn's disease who developed lymphoma. Two additional patients with rheumatoid arthritis and one patient with acquired immunodeficiency syndrome (AIDS) developed lymphomas. It has been argued that the rate of lymphoma observed in clinical trials is consistent with what might be observed in a similar population of rheumatoid arthritis and Crohn's disease patients, particularly those with long-standing and chronically active disease. Observations in larger numbers of treated patients are needed to understand fully the safety of or risks posed by this agent.

Liquid diets for Crohn's disease

In the early 1970's, disease modifying effects of an elemental diet in Crohn's disease were observed. The first controlled study in 1984 confirmed that an elemental diet was as effective as steroids in inducing remission in acute CD. Several subsequent studies supported this primary therapeutic effect for both elemental and polymeric enteral diets. Pooling the data however has shown a less favorable outcome with three meta-analyses similarly concluding that corticosteroids were more effective than enteral diet therapy. Data, from a single center spanning 10 years of enteral diet therapy supported remission rates equal to that of drug therapy. In addition to therapeutic effect, liquid diets for acute CD offer an unrivalled safety profile and significant nutritional benefits. These diets may be ideal therapy in pediatric CD, especially in the presence of malnutrition or growth impairment, and in patients with severe drug induced side effects.

To date, the mechanisms underlying this therapeutic response remain unclear. Proposed theories include reduced antigenic load, provision of trophic amino acids, alterations in gut flora, and immune modulating effects of fatty acids supplied by the feed. The quantity and type of fat in a liquid feed may be an important determinant of therapeutic response, a premise

supported by reports of aberrant fatty acid profiles in CD and better therapeutic outcome with lower fat and fat modified feeds. Specific constituents of an enteral feed may aid mucosal repair and protective mechanisms in CD.



There has been an interest in the role of glutamine, although a recent controlled trial could find no benefit associated with a glutamine enriched polymeric formula in the treatment of CD. In another recent study, butyrate was reported to downregulate inflammatory cytokine expression. In the future, these and other elements, including pre- and probiotics, short chain fatty acids, and growth factors may have a place in a CD specific formula.

Miscellaneous Therapies

Short-Chain Fatty Acids. Short-chain fatty acids (SCFA) are the preferred energy source for colonocytes and are produced by by anaerobes as a consequence of the fermentation of undigested carbohydrates. A defect in SCFA metabolism by colonocytes has been postulated to contribute to ulcerative colitis, and SCFA irrigation is an effective treatment of diversion colitis. Therefore, SCFA supplementation has been tried as a treatment for ulcerative colitis. Studies have used butyrate, the primary colonic fuel, or a mixture of butyrate, acetate, and proprionate delivered as an enema. Uncontrolled studies have suggested modest benefit in mild-to-moderate disease with few side effects. A small, single-blinded, cross-over study of SCFA enemas in patients with active distal ulcerative colitis reportedly resulted in endoscopic improvement in 9 of 10 patients while on therapy but in none while on placebo. Nevertheless, the largest double-blind, placebo-controlled, randomized trial of SCFA enemas did not demonstrate efficacy in active left-sided ulcerative colitis. Other investigators have concentrated on boosting SCFA concentrations by supplying fermentable substrate in nutritional supplements; however, the benefits of this approach in ulcerative colitis have yet to be reported.

Nicotine. The first clinical trials of nicotine in the treatment of ulcerative colitis arose from the epidemiologic observations of an elevated relative risk of the disease in patients who had quit smoking. An initial, double-blind, placebo-controlled study of transdermal nicotine in active colitis reported positive results. Of 72 patients randomized, 48.6% on 15 to 25 mg/d of nicotine had symptomatic remissions versus 24.3% of the placebo group (P=.03). Side effects, such as nausea, lightheadedness, headache, and sleep disturbance, were more common among treated patients. A double-blind, placebo-controlled study of transdermal nicotine in 64 nonsmokers (nearly half of whom were previous smokers) showed clinical improvement in 39% of patients treated with nicotine versus 9% of patients receiving placebo (P=.007) at 4 weeks. In contrast, a randomized, double-blind study of 61 patients with active ulcerative colitis compared treatment with 15 to 25 mg transdermal nicotine as tolerated to prednisolone 15 mg orally daily. Nicotine produced side effects more commonly than prednisolone and was less effective than the low dose of prednisolone used over the 6 weeks of study. Maintenance therapy with nicotine does not appear to be effective.

Subsequent efforts have concentrated on affecting local delivery of nicotine by enemas or delayed-release formulations to

minimize the adverse effects commonly seen with transdermal delivery. Possible explanations for the beneficial effect of nicotine include modulation of proinflammatory cytokines and stimulus of the production of beneficial mucus.

Guidelines

In March 2001, the American College of Gastroenterology published updated guidelines for the management of IBD. These recommenddation will hopefully allow us to maximize the prospects of establishing and maintaining remission in patients with IBD, thereby reducing the need for glucocorticoids and minimizing the risk of complications such as osteoporosis. Following is a quick review of the treatment guidelines for UC and CD.

Guidelines for Ulcerative Colitis

The 5-aminosalicylate agents are considered first-line therapy for mild to moderate UC. Treatment may be administered as topical therapy alone (for distal disease), oral therapy (for extensive disease), or a combination of the two. Of the oral 5-5-aminosalicylate compounds, mesalamine is preferable to sulfasalazine because the therapeutic response is dose-related, but side effects are not. A dose-response relationship exists over a mesalamine dosage range of 2.4 g/d to at least 4.8 g/d (the highest dosage that has been examined in clinical trials). Use of glucocorticoids can be avoided in many cases by optimizing 5-ASA dosage. Patients with moderately severe UC are usually treated with a short course of glucocorticoids. Patients with severe disease require hospitalization and treatment with intravenous (IV) glucocorticoids. Those who do not respond may require IV cyclosporine or colectomy.

Complete remission must be established before maintenance therapy is started for ulcerative colitis. The transition phase should begin with full doses of the treatment used to induce remission. Glucocorticoids should be tapered according to the rapidity of response, and these agents should be tapered before topical mesalamine is tapered in patients receiving combination therapy.

Glucocorticoids are not effective in maintaining remission in UC. If remission has been established with these agents, 5-aminosalicylate agents should be used to maintain remission. Maintenance therapy with sulfasalazine is usually at a dosage of 2 g/d, as opposed to the 4-g/d dosage used to establish remission. This dosage reduction is based on safety rather than efficacy considerations, as a substantial proportion of patients develop side effects at the 4-g/d dosage. In contrast, the efficacy of mesalamine is dose-dependent, but the side effects are not. It is recommended that the same mesalamine dose used to establish remission be used as maintenance therapy.

If a patient with UC is truly glucocorticoid-dependent despite optimal doses of aminosalicylates, then azathioprine or 6-mercaptopurine (6-MP) may be beneficial.

Medical Management of Ulcerative Colitis

Active Disease	Maintenance Therapy
Mild-moderate disease	Distal colitis
Distal Colitis	Sulfasalazine or 5-ASA (oral or topical)*
Sulfasalazine or 5-ASA (oral or topical)*	Azathioprine or 6-MP§
Topical corticosteroid	Extensive colitis
Extensive colitis	Sulfasalazine or oral 5-ASA
Sulfasalazine or oral 5-ASA	Azathioprine or 6-MP§
Moderate-severe disease	
Distal colitis	
Topical or oral 5-ASA	
Topical corticosteroid†	
Prednisone	
Extensive colitis	
Prednisone	
Severe-fulminant disease	
Distal or extensive colitis	
Intravenous corticosteroids	
Intravenous cyclosporine‡	

* Topical 5-ASA may be prescribed alone or in combination with an oral 5-ASA preparation or sulfasalazine

† Topical corticosteroids may be prescribed alone or in combination with an oral 5-ASA preparation or sulfasalazine

‡ Ulcerative colitis patient who fail to respond to intravenous corticosteroids should be considered for cyclosporine or colectomy

§ Used to treat steroid-dependent and steroid-resistant patients

5-ASA = 5-aminosalicyclic acid; 6-MP = 6-mercaptopurine

Guidelines for Crohn's Disease

The selection of therapies for active Crohn's disease should take into consideration the disease location and severity, potential for side effects, responses to previous treatments, and presence of extraintestinal manifestations. Mild to moderate Crohn's disease is treated with oral 5-ASA agents. However, recent data suggest that, when budesoinde becomes available, there may be a role for this agent in the management of patients with mild to moderate active disease. Antibiotics are also used for mild to moderate as well as moderate to severe Crohn's disease, especially in patients with perianal disease and infectious complications. Glucocorticoids are reserved for use in more moderate to severe disease, where 5-ASA agents are not as effective. High-dose cyclosporine is effective for severe Crohn's disease if it is administered intravenously rather than orally. Infliximab is an option for the treatment of Crohn's disease, especially in disease that has been refractory to other agents.

Glucocorticoids should not be used for the maintenance of remission in Crohn's disease. Azathioprine and 6-MP are beneficial for maintenance therapy after remission has been established with glucocorticoids. Evidence suggests that either mesalamine or azathioprine/6-MP should be considered for the prevention of disease recurrence after surgical resection.

Medical Management of Crohn's Disease

Active Disease	Maintenance Therapy«
Mild-moderate disease	Sulfasalazine or 5-ASA
Oral 5-ASA or sulfasalazine *	Metronidazole
Metronidazole or quinolones	Azathioprine or 6-MP
Budesonide	
Prednisone†	
Azathioprine or 6-MP‡	
Infliximab	
Severe disease	
Prednisone	
Intravenous corticosteroids	
TPN or elemental diet	
Infliximab	
Intravenous cyclosporine	
Perianal or fistulizing disease	
Metronidazole or quinolones	
Infliximab	
Intravenous cyclosporine§	

*Agent should target site of active mucosal inflammation

† Initiated when aminosalicylates prove ineffective at maximal doses

‡ Used to treat steroid-dependent and steroid-resistant patients

§ Reserved for patients unresponsive to parenteral corticosteroids or those with severe perianal or fistulous disease

« Agents listed may be effective as maintenance therapies or for prevention of postoperative recurrence

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; TPN = total parenteral nutrition

Conclusions for Treatment of Ulcerative Colitis and Crohn's Disease

Every attempt should be made to establish and maintain remission in IBD, as most complications are related to disease activity. Furthermore, successful treatment of active disease and prevention of relapse will avoid or minimize the need for glucocorticoids, reducing the associated risk of bone loss that can lead to osteoporosis and, eventually, fractures.

Osteoporosis in IBD

Patients with IBD are at increased risk for loss of bone mineral density (BMD), potentially leading to osteoporosis and, ultimately, fractures. Osteoporosis is defined as "a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture." Bone undergoes constant remodeling through a cycle of resorption by osteoclasts and new bone formation by osteoblasts. Remodeling of the entire skeleton occurs approximately every ten years. The skeleton is composed of two types of bones: cortical and trabecular bone. Trabecular bone, found in the vertebrae, ribs, pelvis and long bones, is less dense and more metabolically active than cortical bone. Therefore, trabecular bone is much more vulnerable to the negative influences of inflammation or glucocorticoids in IBD patients.

The best method to assess bone density is by dual-energy x-ray absorptiometry (DEXA) scanning of the femur or spine. Measurement of bone density by DEXA may be reported as T-scores or Z-scores. The T-score is defined as the standard deviation of bone density as compared with the peak bone mass in a young adult. A T

score greater than –1.0 is considered normal, whereas scores of –1.0 to –2.49 define osteopenia, and a score of –2.5 or lower signifies osteoporosis. The Z score is the measurement of bone density adjusted for age, gender and race.

Intrepretation of Bone Density Scores Using DEXA

T Score	Standard deviation of bone density compared with peak bone mass in young adult	
	- Normal	T = 0 to – 0.99 (T > -1.0)
	- Osteopenia	T = -1.0 to –2.49
	- Osteoporosis	T = ≤ -2.5
Z score	Age-, gender-, and race-adjusted measurement	

DEXA = dual-energy x-ray absorptiometry

Data from studies using DEXA have shown that 40% to 50% of patients with IBD have osteopenia and anywhere from 2% to 30% of patients have osteoporosis. Both disorders have generally been observed more frequently in Crohn's disease than in ulcerative colitis, possibly because of small bowel malabsorption of calcium and vitamin D in Crohn's. Alternatively, the higher rate observed in CD may result from decreased calcium intake due to lactase deficiency or strictures. Another possibility is that patients with CD are more likely to receive chronic therapy with glucocorticoids, which reduce BMD.

In a study of men and premenopausal women taking glucocorticoids for at least 3 months with CD (n=26) or UC (n=23), osteopenia (defined as a Z score $\leq$1.0) was present in nearly half the UC group and an even higher proportion of the CD group. On multivariate analysis, the use of glucocorticoids was the only significant independent predictor of osteopenia ($P \leq .025$).

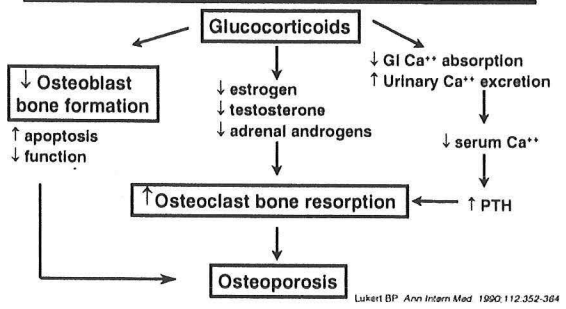
Risk of Fracture. Fracture is a more appropriate end point than BMD in studies of osteoporosis. In a population-base study assessing fracture risk in IBD, the rate of fractures at all sites combined was 98.8 per 10,000 persons in IBD patients. The rate in CD (86.2/10,000 persons) was not significantly different from that in UC (112.4/10,000 persons). The incidence rate ratio of fractures at all sites combined (hip, spine, rib, and wrist/forearm) was 1.41 in IBD patients compared to controls, reflecting an increase rate of fracture of approximately 40%. No difference in the degree of elevated risk was apparent between men and women with CD vs. UC. In UC, however, the incidence rate ratio was significantly higher for men than for women. These data demonstrates that the risk of osteoporosis-related fracture in IBD is not confined to women.

Risk Factors for Fracture in IBD. Patients with IBD are subject to the same general risk factors for osteoporosis as the general population. However, IBD is also associated with specific factors that can increase the risk of osteoporosis. These include certain medications (glucocorticoids, cyclosporine, or methotrexate), inflammatory factors (interleukin-6 [IL-6], IL-1, and tumor necrosis factor), malabsorption or malnutrition (altering levels of vitamin D and calcium), hyperalimentation, hypogonadism, and the type of IBD. With regard to the latter issue, some studies have suggested that the prevalence of osteoporosis is similar in CD and UC, whereas other work has shown that osteoporosis is more common in CD than in UC.

Vitamin D deficiency is estimated to occur in 30% to 60% of patients with CD. Factors leading to such deficiency include reduced intake of dairy products supplemented by vitamin D, malabsorption of vitamin D due to small bowel disease or short bowel syndrome, and bacteria overgrowth or use of cholestyramine, resulting in steatorrhea.

The mechanisms of glucocorticoid-induced osteoporosis entail enhanced bone resorption and reduced bone formation. Bone resorption increases because of reduced intestinal calcium absorption, increased renal calcium excretion, increased parathyroid hormone secretion, reduced calcitonin synthesis, increased osteoclastic activity, and enhanced binding of macrophages to bone. Bone formation is reduced because of decreased synthesis and proliferation of osteoblasts as well as impaired gonadal hormone production. Bone loss can occur as early as 2 to 3 months after the initiation of glucocorticoid therapy. The cumulative dose and duration of treatment may also affect the degree of risk.

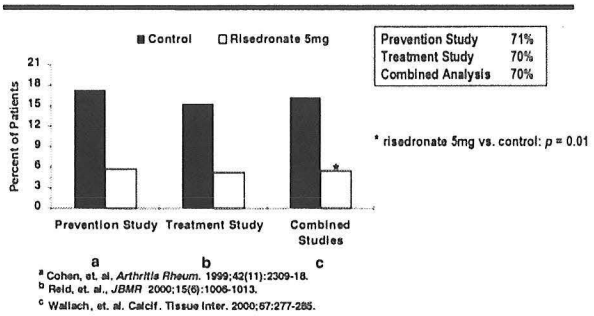
Pathophysiology of Glucocorticoid-Induced Osteoporosis



Prevention and Treatment of Osteoporosis in IBD. Glucocorticoid-sparing strategies should be employed to minimize the adverse impact of steroids whenever possible. Maximum doses of 5-aminosalicyclic acid (5-ASA) agents (eg, mesalamine 4.8 g/d) should be administered before resorting to glucocorticoids. Close adherence to 5-ASA regimens can increase the likelihood of establishing remission and can minimize the possibility that patients will ultimately require glucocorticoids. Mesalamine offers an advantage over sulfasalazine with regard to the prospect of good compliance. In contrast to treatment with sulfasalazine, the risk of side effects with mesalamine is not dose-related. When glucocorticoids cannot be avoided, they should be used in the lowest possible doses or on alternate days, if feasible. Other methods of reducing the requirement for glucocorticoids include immunotherapy with azathioprine, 6-mercaptopurine (6-MP), as well as methotrexate, infliximab, or surgery.

Despite the above measures directed at controlling IBD, some patients will require additional measures that directly impact bone metabolism. The options available for the prevention and treatment of glucocorticoid-induced osteoporosis (GIO) include calcium and vitamin D supplementation, hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), cacitonin, and bisphosphonates.

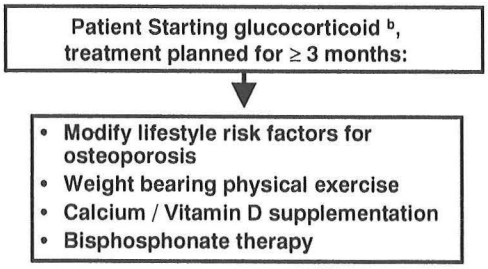
Vertebral Fracture Incidence in Glucocorticoid-Induced Osteoporosis at 1 Year



Supplementation with calcium and vitamin D should be tried first; however, although important, it often is not sufficient to prevent bone loss in many patients taking glucocorticoids. Estrogen is not approved for the prevention or treatment of GIO. No data have demonstrated a decreased fracture risk with estrogen therapy. Conjugated estrogens are approved only for the prevention, not the treatment, of postmenopausal osteoporosis, as no controlled studies have shown a reduced fracture risk in the latter setting. An important point, however, is that hypogonadism is a frequent and

underrecognized complication of chronic glucocorticoid treatment. In cases of documented hypogonadism, estrogen should be replaced in women and testosterone in men. Raloxifene is the first SERM to be approved by the US Food and Drug Administration (FDA) for the prevention and treatment of postmenopausal osteoporosis. No data are available on the effect of raloxifene in patients taking glucocorticoids, and the agent is not approved for the prevention or treatment of osteoporosis in this setting. Of the available therapies, only the bisphosphonates have demonstrated efficacy in GIO. Risedronate is approved for the prevention and treatment of GIO and alendronate is approved for the treatment of this condition.

Recommendation for Prevention and Treatment of Glucocorticoid-Induced Osteoporosis [a]

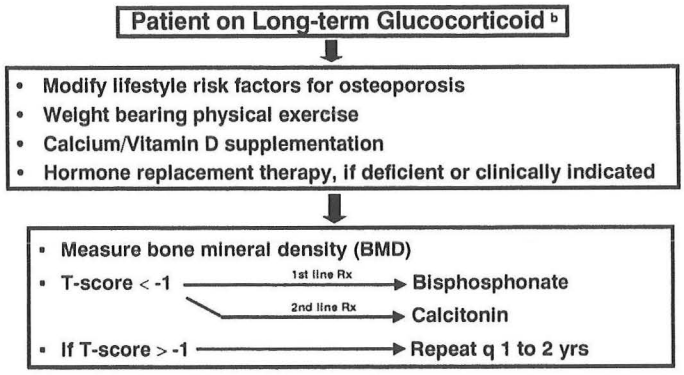


[a] American College of Rheumatology Guidelines for Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis and Rheumatism. 2001; 44: 1496-1503

[b] Prednisone equivalent of 5 mg/day

If glucocorticoids cannot be avoided, preventive measures should be instituted according to the extent of the risk as identified by DEXA. Both the risk and the rate of bone loss may be ameliorated through the use of preventive measures such as calcium and vitamin D supplementation, weight-bearing exercise regimens, smoking cessation, reduced alcohol consumption, bisphosphonates, and hormonal therapy for postmenopausal women. These measures should, in fact, be instituted for the prevention of osteoporosis in all patients with IBD, regardless of whether glucocorticoid therapy is present as an additional risk factor.

Recommendation for Prevention and Treatment of Glucocorticoid-Induced Osteoporosis [a]



[a] ACR Guidelines for Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis and Rheumatism 2001; 44: 1496-1503.

[b] Prednisone equivalent of 5 mg/day

Screening for Osteoporosis in IBD. IBD patients not taking steroids are also at risk for development of osteoporosis. However, criteria for selecting these IBD patients for bone densitometry have not yet been determined. Some have suggested that the most cost-effective approach would be to limit screening to high-risk patients – for instance, older individuals or those with preexisting fractures. Others propose a more aggressive approach in which all IBD patients are screened in an effort to prevent the adverse consequences of bone loss. Debate also continues with regard to the optimal timing of screening. However, the current consensus holds that men and women should undergo baseline evaluations early in the course of their clinical management for IBD, then follow-up assessments to check for changes at 6 and 12 months. Depending on the outcome in this follow-up period, one could initiate therapy and report yearly until stable. However, if there is no sign of change over that time period, then screening every 3 years appears appropriate.

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